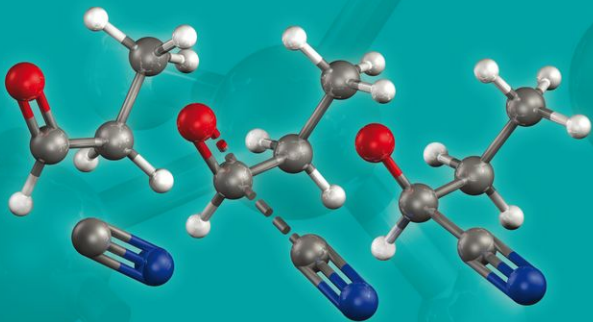# ORGANIC
CHEMISTRY

Jonathan Clayden, Nick Greeves, and Stuart Warren

Organic Chemistry

@ Organic Chemistry—online support

Each chapter in this book is accompanied by a set of problems, which are available free of charge online. To access them visit the Online Resource Centre at **www.oxfordtextbooks.co.uk/orc/clayden2e/** and enter the following:
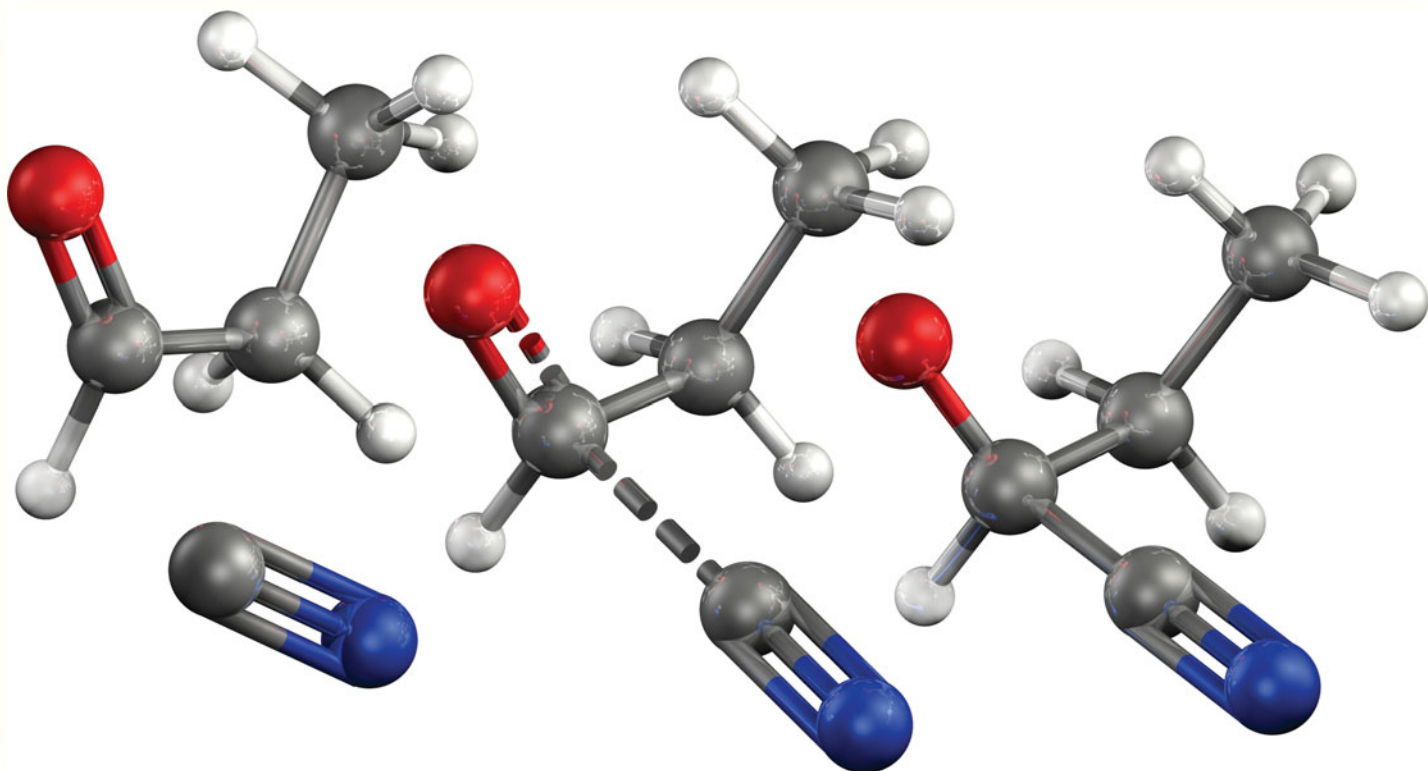
Username: clayden2e
Password: compound

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ORGANIC
CHEMISTRY

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Brief contents

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Abbreviations

Ac	Acetyl		**DMS**	Dimethyl sulfide
Acac	Acetylacetonate		**DMSO**	Dimethyl sulfoxide
AD	Asymmetric dihydroxylation		**DNA**	Deoxyribonucleic acid
ADP	Adenosine 52-diphosphate		**E1**	Unimolecular elimination
AE	Asymmetric epoxidation		**E2**	Bimolecular elimination
AIBN	Azobisisobutyronitrile		**E$_a$**	Activation energy
AO	Atomic orbital		**EDTA**	Ethylenediaminetetraacetic acid
Ar	Aryl		**EPR**	Electron paramagnetic resonance
ATP	Adenosine triphosphate		**ESR**	Electron spin resonance
9-BBN	9-Borabicyclo[3.3.1]nonane		**Et**	Ethyl
BHT	Butylated hydroxy toluene (2,6-di-*t*-butyl-4-methylphenol)		**FGI**	Functional group interconversion
			Fmoc	Fluorenylmethyloxycarbonyl
BINAP	Bis(diphenylphosphino)-1,1′-binaphthyl		**GAC**	General acid catalysis
			GBC	General base catalysis
Bn	Benzyl		**HMPA**	Hexamethylphosphoramide
Boc, BOC	*tert*-Butyloxycarbonyl		**HMPT**	Hexamethylphosphorous triamide
Bu	Butyl		**HOBt**	1-Hydroxybenzotriazole
***s*-Bu**	*sec*-Butyl		**HOMO**	Highest occupied molecular orbital
***t*-Bu**	*tert*-Butyl		**HPLC**	High performance liquid chromatography
Bz	Benzoyl			
Cbz	Carboxybenzyl		**HIV**	Human immunodeficiency virus
CDI	Carbonyldiimidazole		**IR**	Infrared
CI	Chemical ionization		**KHMDS**	Potassium hexamethyldisilazide
CoA	Coenzyme A		**LCAO**	Linear combination of atomic orbitals
COT	Cyclooctatetraene		**LDA**	Lithium diisopropylamide
Cp	Cyclopentadienyl		**LHMDS**	Lithium hexamethyldisilazide
DABCO	1,4-Diazabicyclo[2.2.2]octane		**LICA**	Lithium isopropylcyclohexylamide
DBE	Double bond equivalent		**LTMP, LiTMP**	Lithium 2,2,6,6-tetramethylpiperidide
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene		**LUMO**	Lowest unoccupied molecular orbital
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene		***m*-CPBA**	*meta*-Chloroperoxybenzoic acid
DCC	*N,N*-dicyclohexylcarbodiimide		**Me**	Methyl
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone		**MO**	Molecular orbital
			MOM	Methoxymethyl
DEAD	Diethyl azodicarboxylate		**Ms**	Methanesulfonyl (mesyl)
DIBAL	Diisobutylaluminum hydride		**NAD**	Nicotinamide adenine dinucleotide
DMAP	4-Dimethylaminopyridine		**NADH**	Reduced NAD
DME	1,2-Dimethoxyethane		**NBS**	*N*-Bromosuccinimide
DMF	*N,N*-Dimethylformamide		**NIS**	*N*-Iodosuccinimide
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone		**NMO**	*N*-Methylmorpholine-*N*-oxide

NMR	Nuclear magnetic resonance		**SOMO**	Singly occupied molecular orbital
NOE	Nuclear Overhauser effect		**STM**	Scanning tunnelling microscopy
PCC	Pyridinium chlorochromate		**TBDMS**	*Tert*-butyldimethylsilyl
PDC	Pyridinium dichromate		**TBDPS**	*Tert*-butyldiphenylsilyl
Ph	Phenyl		**Tf**	Trifluoromethanesulfonyl (triflyl)
PPA	Polyphosphoric acid		**THF**	Tetrahydrofuran
Pr	Propyl		**THP**	Tetrahydropyran
i-**Pr**	*iso*-Propyl		**TIPS**	Triisopropylsilyl
PTC	Phase transfer catalysis		**TMEDA**	*N,N,N′,N′*-tetramethyl-1,2-ethylenediamine
PTSA	*p*-Toluenesulfonic acid		**TMP**	2,2,6,6-Tetramethylpiperidine
Py	Pyridine		**TMS**	Trimethylsilyl, tetramethylsilane
Red Al	Sodium *bis*(2-methoxyethoxy) aluminum hydride		**TMSOTf**	Trimethylsilyl triflate
RNA	Ribonucleic acid		**TPAP**	Tetra-*N*-propylammonium perruthenate
SAC	Specific acid catalysis		**Tr**	Triphenylmethyl (trityl)
SAM	*S*-Adenosyl methionine		**TS**	Transition state
SBC	Specific base catalysis		**Ts**	*p*-Toluenesulfonyl, tosyl
S$_N$1	Unimolecular nucleophilic substitution		**UV**	Ultraviolet
S$_N$2	Bimolecular nucleophilic substitution		**VSEPR**	Valence shell electron pair repulsion

Preface to the second edition

Students of chemistry are not hard-pressed to find a text to support their learning in organic chemistry through their years at university. The shelves of a university bookshop will usually offer a choice of at least half a dozen—all entitled 'Organic Chemistry', all with substantially more than 1000 pages. Closer inspection of these titles quickly disappoints expectations of variety. Almost without exception, general organic chemistry texts have been written to accompany traditional American sophomore courses, with their rather precisely defined requirements. This has left the authors of these books little scope for reinvigorating their presentation of chemistry with new ideas.

We wanted to write a book whose structure grows from the development of ideas rather than being dictated by the sequential presentation of facts. We believe that students benefit most of all from a book which leads from familiar concepts to unfamiliar ones, not just encouraging them to *know* but to *understand* and to understand *why*. We were spurred on by the nature of the best modern university chemistry courses, which themselves follow this pattern: this is after all how science itself develops. We also knew that if we did this we could, from the start, relate the chemistry we were talking about to the two most important sorts of chemistry that exist—the chemistry that is known as life, and the chemistry as practised by chemists solving real problems in laboratories.

We aimed at an approach which would make sense to and appeal to today's students. But all of this meant taking the axe to the roots of some long-standing textbook traditions. The best way to find out how something works is to take it apart and put it back together again, so we started with the tools for expressing chemical ideas: structural diagrams and curly arrows. Organic chemistry is too huge a field to learn even a small part by rote, but with these tools, students can soon make sense of chemistry which may be unfamiliar in detail by relating it to what they know and understand. By calling on curly arrows and ordering chemistry according to mechanism we allow ourselves to discuss mechanistically (and orbitally) simple reactions (addition to C=O, for example) before more complex and involved ones (such as S_N1 and S_N2).

Complexity follows in its own time, but we have deliberately omitted detailed discussion of obscure reactions of little value, or of variants of reactions which lie a simple step of mechanistic logic from our main story: some of these are explored in the problems associated with each chapter, which are available online.[1] We have similarly aimed to avoid exhuming principles and rules (from those of Le Châtelier through Markovnikov, Saytseff, least motion, and the like) to explain things which are better understood in terms of unifying fundamental thermodynamic or mechanistic concepts.

All science must be underpinned by evidence, and support for organic chemistry's claims is provided by spectroscopy. For this reason we first reveal to students the facts which spectroscopy tells us (Chapter 3) before trying to explain them (Chapter 4) and then use them to deduce mechanisms (Chapter 5). NMR in particular forms a significant part of four chapters in the book, and evidence drawn from NMR underpins many of the discussions right through the book. Likewise, the mechanistic principles we outline in Chapter 5, firmly based in the orbital theories of Chapter 4, underpin all of the discussion of new reactions through the rest of the book.

We have presented chemistry as something whose essence is truth, of provable veracity, but which is embellished with opinions and suggestions to which not all chemists subscribe. We aim to avoid dogma and promote the healthy weighing up of evidence, and on occasion we are content to leave readers to draw their own conclusions. Science is important not just to scientists, but to society. Our aim has been to write a book which itself takes a scientific

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[1] See www.oxfordtextbooks.co.uk/orc/clayden2e/.

standpoint—'one foot inside the boundary of the known, the other just outside'[2]—and encourages the reader to do the same.

The authors are indebted to the many supportive and critical readers of the first edition of this book who have supplied us over the last ten years with a stream of comments and corrections, hearty encouragements and stern rebukes. All were carefully noted and none was overlooked while we were writing this edition. In many cases these contributions helped us to correct errors or make other improvements to the text. We would also like to acknowledge the support and guidance of the editorial team at OUP, and again to recognize the seminal contribution of the man who first nurtured the vision that organic chemistry could be taught with a book like this, Michael Rodgers. The time spent on the preparation of this edition was made available only with the forbearance of our families, friends and research groups, and we thank all of them for their patience and understanding.

Changes for this edition

In the decade since the publication of the first edition of this book it has become clear that some aspects of our original approach were in need of revision, some chapters in need of updating with material which has gained in significance over those years, and others in need of shortening. We have taken into account a consistent criticism from readers that the early chapters of the first edition were too detailed for new students, and have made substantial changes to the material in Chapters 4, 8, and 12, shifting the emphasis towards explanation and away from detail more suitably found in specialised texts. Every chapter has been rewritten to improve clarity and new explanations and examples have been used widely. The style, location, and content of the spectroscopy chapters (3, 13, 18, and 31) have been revised to strengthen the links with material appearing nearby in the book. Concepts such as conjugate addition and regioselectivity, which previously lacked coherent presentation, now have their own chapters (22 and 24). In some sections of the first edition, groups of chapters were used to present related material: these chapter groups have now been condensed—so, for example, Chapters 25 and 26 on enolate chemistry replace four previous chapters, Chapters 31 and 32 on cyclic molecules replace three chapters, Chapter 36 on rearrangements and fragmentations replaces two chapters, and Chapter 42 on the organic chemistry of life replaces three chapters (the former versions of which are available online). Three chapters placed late in the first edition have been moved forward and revised to emphasize links between their material and the enolate chemistry of Chapters 25 and 26, thus Chapter 27 deals with double-bond stereocontrol in the context of organo-main group chemistry, and Chapters 29 and 30, addressing aromatic heterocycles, now reinforce the link between many of the mechanisms characteristic of these compounds and those of the carbonyl addition and condensation reactions discussed in the previous chapters. Earlier discussion of heterocycles also allows a theme of cyclic molecules and transition states to develop throughout Chapters 29–36, and matches more closely the typical order of material in undergraduate courses.

Some fields have inevitably advanced considerably in the last 10 years: the chapters on organometallic chemistry (40) and asymmetric synthesis (41) have received the most extensive revision, and are now placed consecutively to allow the essential role of organometallic catalysis in asymmetric synthesis to come to the fore. Throughout the book, new examples, especially from the recent literature of drug synthesis, have been used to illustrate the reactions being discussed.

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[2] McEvedy, C. The Penguin Atlas of Ancient History, Penguin Books, 1967.

Organic chemistry and this book

You can tell from the title that this book tells you about organic chemistry. But it tells you more than that: it tells you *how we know* about organic chemistry. It tells you facts, but it also teaches you how to find facts out. It tells you about reactions, and teaches you how to predict which reactions will work; it tells you about molecules, and it teaches you how to work out ways of making them.

We said 'it tells' in that last paragraph. Maybe we should have said 'we tell' because we want to speak to you through our words so that you can see how we think about organic chemistry and to encourage you to develop your own ideas. We expect you to notice that three people have written this book, and that they don't all think or write in the same way. That is as it should be. Organic chemistry is too big and important a subject to be restricted by dogmatic rules. Different chemists think in different ways about many aspects of organic chemistry and in many cases it is not yet, and may never be, possible to be sure who is right. In many cases it doesn't matter anyway.

We may refer to the history of chemistry from time to time but we are usually going to tell you about organic chemistry as it is now. We will develop the ideas slowly, from simple and fundamental ones using small molecules to complex ideas and large molecules. We promise one thing. We are not going to pull the wool over your eyes by making things artificially simple and avoiding the awkward questions. We aim to be honest and share both our delight in good complete explanations and our puzzlement at inadequate ones.

The chapters

So how are we going to do this? The book starts with a series of chapters on the structures and reactions of simple molecules. You will meet the way structures are determined and the theory that explains those structures. It is vital that you realize that theory is used to explain what is known by experiment and only then to predict what is unknown. You will meet mechanisms—the dynamic language used by chemists to talk about reactions—and of course some reactions.

The book starts with an introductory section of four chapters:

1. What is organic chemistry?
2. Organic structures
3. Determining organic structures
4. Structure of molecules

Chapter 1 is a 'rough guide' to the subject—it will introduce the major areas where organic chemistry plays a role, and set the scene by showing you some snapshots of a few landmarks. In Chapter 2 you will look at the way in which we present diagrams of molecules on the printed page. Organic chemistry is a visual, three-dimensional subject and the way you draw molecules shows how you think about them. We want you too to draw molecules in the best way possible. It is just as easy to draw them well as to draw them in an old-fashioned or inaccurate way.

Then in Chapter 3, before we come to the theory which *explains* molecular structure, we shall introduce you to the experimental techniques which *tell us about* molecular structure. This means studying the interactions between molecules and radiation by spectroscopy—using the whole electromagnetic spectrum from X-rays to radio waves. Only then, in Chapter 4, will we go behind the scenes and look at the theories of why atoms combine in the ways they do. Experiment comes before explanation. The spectroscopic methods of Chapter 3 will still be telling the truth in a hundred years' time, but the theories of Chapter 4 will look quite dated by then.

We could have titled those three chapters:

2. What shapes do organic molecules have?
3. How do we know they have those shapes?
4. Why do they have those shapes?

You need to have a grasp of the answers to these three questions before you start the study of organic reactions. That is exactly what happens next. We introduce organic reaction mechanisms in Chapter 5. Any kind of chemistry studies reactions—the transformations of molecules into other molecules. The dynamic process by which this happens is called *mechanism* and is the grammar of organic chemistry—the way that one molecule can change into another. We want you to start learning and using this language straight away so in Chapter 6 we apply it to one important class of reaction. We therefore have:

5. Organic reactions
6. Nucleophilic addition to the carbonyl group

Chapter 6 reveals how we are going to subdivide organic chemistry. We shall use a mechanistic classification rather than a structural classification and explain one type of *reaction* rather than one type of *compound* in each chapter. In the rest of the book most of the chapters describe types of reaction in a mechanistic way. Here is a selection from the first half of the book:

9. Using organometallic reagents to make C—C bonds
10. Nucleophilic substitution at the carbonyl group
11. Nucleophilic substitution at C=O with loss of carbonyl oxygen
15. Nucleophilic substitution at saturated carbon
17. Elimination reactions
19. Electrophilic addition to alkenes
20. Formation and reactions of enols and enolates
21. Electrophilic aromatic substitution
22. Conjugate addition and nucleophilic aromatic substitution

Interspersed with these chapters are others on physical aspects of molecular structure and reactivity, stereochemistry, and structural determination, which allow us to show you how we know what we are telling you is true and to explain reactions intelligently.

7. Delocalization and conjugation
8. Acidity, basicity, and pK_a
12. Equilibria, rates, and mechanisms
13. ¹H NMR: proton nuclear magnetic resonance
14. Stereochemistry
16. Conformational analysis
18. Review of spectroscopic methods

By the time we reach the end of Chapter 22 you will have met most of the important ways in which organic molecules react with one another, and we will then spend two chapters revisiting some of the reactions you have met before in two chapters on selectivity: how to get the reaction you want to happen and avoid the reaction you don't.

23. Chemoselectivity and protecting groups
24. Regioselectivity

The materials are now in place for us to show you how to make use of the reaction mechanisms you have seen. We spend four chapters explaining some ways of using carbonyl chemistry and the chemistry of Si, S, and P to make C—C and C=C bonds. We then bring this all together with a chapter which gives you the tools to work out how you might best set about making any particular molecule.

25. Alkylation of enolates

26. Reactions of enolates with carbonyl compounds: the aldol and Claisen reactions

27. Sulfur, silicon, and phosphorus in organic chemistry

28. Retrosynthetic analysis

Most organic compounds contain rings, and many cyclic structures entail one of two aspects which are rather special: aromaticity and well-defined conformations. The next group of chapters leads you through the chemistry of ring-containing compounds to the point where we have the tools to explain why even acyclic molecules react to give products with certain spatial features.

29. Aromatic heterocycles 1: reactions

30. Aromatic heterocycles 2: synthesis

31. Saturated heterocycles and stereoelectronics

32. Stereoselectivity in cyclic molecules

33. Diasteroselectivity

We said that Chapter 22 marks the point where most of the important ways in which molecules react together have been introduced—most but not all. For the next section of the book we survey a range of rather less common but extremely important alternative mechanisms, finishing with a chapter that tells you how we can find out what mechanism a reaction follows.

34. Pericyclic reactions 1: cycloadditions

35. Pericyclic reactions 2: sigmatropic and electrocyclic reactions

36. Participation, rearrangement, and fragmentation

37. Radical reactions

38. Synthesis and reactions of carbenes

39. Determining reaction mechanisms

The last few chapters of the book take you right into some of the most challenging roles that organic chemistry has been called on to play, and in many cases tell you about chemistry discovered only in the last few years. The reactions in these chapters have been used to make the most complex molecules ever synthesized, and to illuminate the way that organic chemistry underpins life itself.

40. Organometallic chemistry

41. Asymmetric synthesis

42. Organic chemistry of life

43. Organic chemistry today

'Connections' sections

That's a linear list of 43 chapters, but chemistry is not a linear subject! It is impossible to work through the whole field of organic chemistry simply by starting at the beginning and working through to the end, introducing one new topic at a time, because chemistry is a network of interconnecting ideas. But, unfortunately, a book is, by nature, a beginning-to-end sort of thing. We have arranged the chapters in a progression of difficulty as far as is possible, but to help you find your way around we have included at the beginning of each chapter a 'Connections' section. This tells you three things divided among three columns:

 (a) The 'Building on' column: what you should be familiar with before reading the chapter—in other words, which previous chapters relate directly to the material within the chapter.

 (b) The 'Arriving at' column: a guide to what you will find within the chapter.

 (c) The 'Looking forward to' column: signposting which chapters later in the book fill out and expand the material in the chapter.

The first time you read a chapter, you should really make sure you have read any chapter mentioned under (a). When you become more familiar with the book you will find that the links highlighted in (a) and (c) will help you see how chemistry interconnects with itself.

Boxes and margin notes

The other things you should look out for throughout the text are the margin notes and boxes. There are four sorts:

> ● **The most important box looks like this. Anything in this sort of box is a key concept or a summary. It's the sort of thing you would do well to hold in your mind as you read or to note down as you learn.**

■ Sometimes the main text of the book needs clarification or expansion, and this sort of margin note will contain such little extras to help you understand difficult points. It will also remind you of things from elsewhere in the book that illuminate what is being discussed. You would do well to read these notes the first time you read the chapter, although you might choose to skip them later as the ideas become more familiar.

> Boxes like this will contain additional examples, amusing background information, and similar interesting, but maybe inessential, material. The first time you read a chapter, you might want to miss out this sort of box, and only read them later on to flesh out some of the main themes of the chapter.

Online support

Organic structures and organic reactions are three-dimensional (3D), and as a complement to the necessarily two-dimensional representations in this book we have developed a comprehensive online resource to allow you to appreciate the material in three dimensions. ChemTube3D contains interactive 3D animations and structures, with supporting information, for some of the most important topics in organic chemistry, to help you master the concepts presented in this book. Online resources are flagged on the pages to which they relate by an icon in the margin. Each web page contains some information about the reaction and an intuitive interactive reaction scheme that controls the display. 3D curly arrows indicate the reaction mechanism, and the entire sequence from starting materials via transition state to products is displayed with animated bond-breaking and forming, and animated charges and lone pairs. The entire process is under the control of you, the user, and can be viewed in three dimensions from any angle. The resizable window button produces a larger window with a range of control options and the molecular photo booth allows you to make a permanent record of the view you want.

🖱 This icon indicates that related interactive resources are available online. A full explanation of how to find these resources is given in a purple panel on the first page of each chapter

ChemTube3D uses Jmol to display the animations so users can interact with the animated 3D structures using the pop-up menu or console using only a web browser. It is ideal for personalized learning and open-ended investigation is possible. We suggest that you make use of the interactive resources once you have read the relevant section of the book to consolidate your understanding of chemistry and enhance your appreciation of the importance of spatial arrangements.

Substantial modifications were made in the writing of this new edition, including the loss or contraction of four chapters found towards the end of the first edition. To preserve this material for future use, the following four chapters from the first edition are available for download from the book's website at www.oxfordtextbooks.co.uk/orc/clayden2e/:

- The chemistry of life
- Mechanisms in biological chemistry
- Natural products
- Polymerization

Further reading

At the end of each chapter, you may find yourself wanting to know more about the material it covers. We have given a collection of suggested places to look for this material—other books, or reviews in the chemical literature, or even some original research papers. There are thousands of examples in this book, and in most cases we have not directed you to the reports of the original work—this can usually be found by a simple electronic database search. Instead, we have picked out publications which seem most interesting, or relevant. If you want an encyclopaedia of organic chemistry, this is not the book for you. You would be better turning to one such as *March's Advanced Organic Chemistry* (M. B. Smith and J. March, 6th edn, Wiley, 2007), which contains thousands of references.

Problems

You can't learn all of organic chemistry—there's just too much of it. You can learn trivial things like the names of compounds but that doesn't help you understand the principles behind the subject. You have to *understand* the principles because the only way to tackle organic chemistry is to learn to work it out. That is why we have provided problems, which you can access from the book's web site. They are to help you discover if you have understood the material presented in each chapter.

If a chapter is about a certain type of organic reaction, say elimination reactions (Chapter 19), the chapter itself will describe the various ways ('mechanisms') by which the reaction can occur and it will give definitive examples of each mechanism. In Chapter 19 there are three mechanisms and about 60 examples altogether. You might think that this is rather a lot but there are in fact millions of examples known of these three mechanisms and Chapter 19 barely scrapes the surface. The problems will help you make sure that your understanding is sound, and that it will stand up to exposure to the rigours of explaining real-life chemistry.

In general, the 10–15 problems at the end of each chapter start easy and get more difficult. They come in two or three sorts. The first, generally shorter and easier, allow you to revise the material in that chapter. They might revisit examples from the chapter to check that you can use the ideas in familiar situations. The next few problems might develop specific ideas from different parts of the chapter, asking you, for example, why one compound reacts in one way while a similar one behaves quite differently. Finally, you will find some more challenging problems asking you to extend the ideas to unfamiliar molecules, and, especially later in the book, to situations which draw on the material from more than one chapter.

The end-of-chapter problems should set you on your way but they are not the end of the journey to understanding. You are probably reading this text as part of a university course and you should find out what kind of examination problems your university uses and practise them too. Your tutor will be able to advise you on suitable problems to help you at each stage of your development.

To access the problems just visit www.oxfordtextbooks.co.uk/orc/clayden2e. The problems are available free of charge; you'll just need the username and password given at the very front of this book

The solutions manual

The problems would be of little use to you if you could not check your answers. For maximum benefit, you need to tackle some or all of the problems as soon as you have finished each chapter without looking at the answers. Then you need to compare your suggestions with ours. You will find our suggestions in the accompanying solutions manual, where each problem is discussed in some detail. (You can buy the solutions manual separately from this book.) The purpose of the problem is first stated or explained. Then, if the problem is a simple one, the answer is given. If the problem is more complex, a discussion of possible answers follows with some comments on the value of each. There may be a reference to the source of the problem so that you can read further if you wish.

Colour

If you have flicked forward through the pages of this book, you will already have noticed something unusual: almost all of the chemical structures are shown in red. This is quite intentional: emphatic red underlines the message that structures are more important than words in organic chemistry. But sometimes small parts of structures are in other colours: here are two examples from p. 12, where we talk about organic compounds containing elements other than C and H.
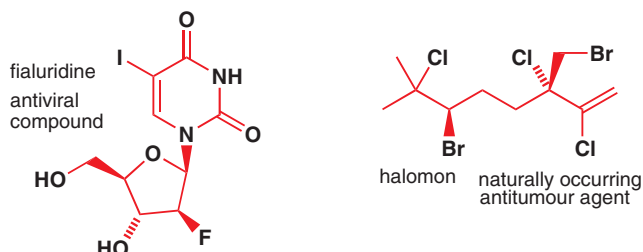
Why are the atom labels black? Because we wanted them to stand out from the rest of the molecule. In general you will see black used to highlight the important details of a molecule—they may be the groups taking part in a reaction, or something that has changed as a result of the reaction, as in these examples from Chapters 9 and 17.
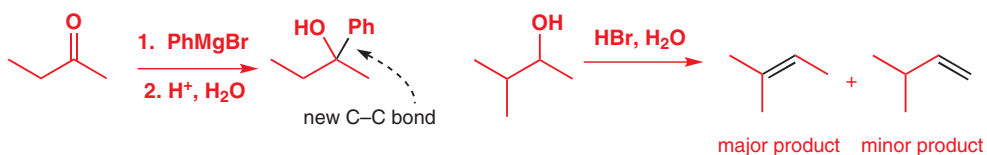
We shall often use black to emphasize 'curly arrows', devices that show the movement of electrons, and whose use you will learn about in Chapter 5. Here are examples from Chapters 11 and 22: notice black also helps the ' + ' and '–' charges to stand out.
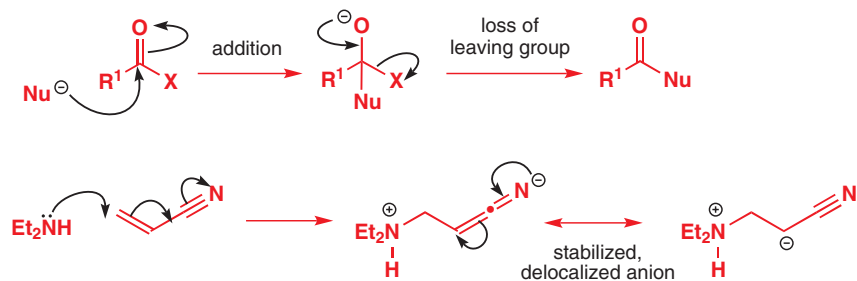
Occasionally, we shall use other colours, such as green, orange, or brown, to highlight points of secondary importance. This example is part of a reaction taken from Chapter 19: we want to show that a molecule of water (H_2O) is formed. The green atoms show where the water comes from. Notice black curly arrows and a new black bond.
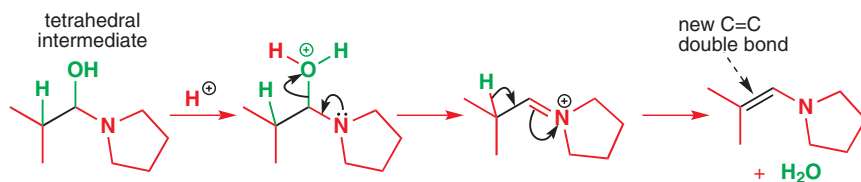
Other colours come in when things get more complicated—in this Chapter 21 example, we want to show two possible outcomes of a reaction: the brown and the orange arrows show the two alternatives, with the green highlighting the deuterium atom remaining in both cases.

less stable keto form   stable enol form of phenol
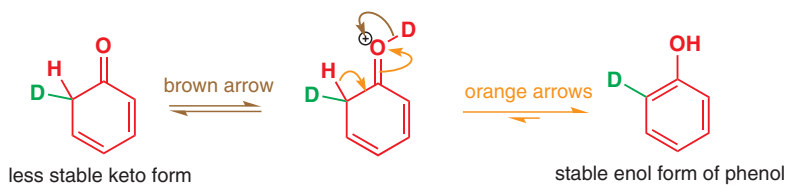
And, in Chapter 14, colour helps us highlight the difference between carbon atoms carrying four different groups and those with only three different groups. The message is: if you see something in a colour other than red, take special note—the colour is there for a reason.
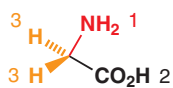
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What is organic chemistry?

Organic chemistry and you

You are already a highly skilled organic chemist. As you read these words, your eyes are using an organic compound (retinal) to convert visible light into nerve impulses. When you picked up this book, your muscles were doing chemical reactions on sugars to give you the energy you needed. As you understand, gaps between your brain cells are being bridged by simple organic molecules (neurotransmitter amines) so that nerve impulses can be passed around your brain. And you did all that without consciously thinking about it. You do not yet understand these processes in your mind as well as you can carry them out in your brain and body. You are not alone there. No organic chemist, however brilliant, understands the detailed chemical working of the human mind or body very well.

We, the authors, include ourselves in this generalization, but we are going to show you in this book what enormous strides have been taken in the understanding of organic chemistry since the science came into being in the early years of the nineteenth century. Organic chemistry began as a tentative attempt to understand the chemistry of life. It has grown into the confident basis of worldwide activities that feed, clothe, and cure millions of people without their even being aware of the role of chemistry in their lives. Chemists cooperate with physicists and mathematicians to understand how molecules behave and with biologists to understand how interactions between molecules underlie all of life. The enlightenment brought by chemistry in the twentieth century amounted to a revolution in our understanding of the molecular world, but in these first decades of the twenty-first century the revolution is still far from complete. We aim not to give you the measurements of the skeleton of a dead science but to equip you to understand the conflicting demands of an adolescent one.

Like all sciences, chemistry has a unique place in our pattern of understanding of the universe. It is the science of molecules. But organic chemistry is something more. It literally creates itself as it grows. Of course we need to study the molecules of nature both because they are interesting in their own right and because their functions are important to our lives. Organic chemistry has always been able to illuminate the mechanisms of life by making new molecules that give information not available from the molecules actually present in living things.

This creation of new molecules has given us new materials such as plastics to make things with, new dyes to colour our clothes, new perfumes to wear, new drugs to cure diseases. Some people think some of these activities are unnatural and their products dangerous or unwholesome. But these new molecules are built by humans from other molecules found naturally on earth using the skills inherent in our natural brains. Birds build nests; people build houses. Which is unnatural? To the organic chemist this is a meaningless distinction. There are toxic compounds and nutritious ones, stable compounds and reactive ones—but there is only one type of chemistry: it goes on both inside our brains and bodies, and also in our flasks and reactors, born from the ideas in our minds and the skill in our hands. We are not going to set ourselves up as moral judges in any way. We believe it is right to try and understand the world

11-*cis*-retinal
absorbs light and allows vision

serotonin
human neurotransmitter
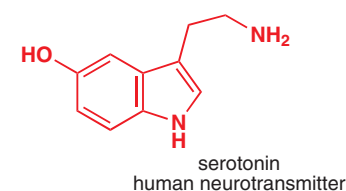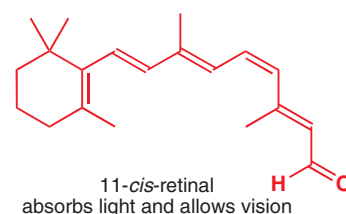
■ We are going to illustrate this chapter with the structures of the organic compounds we talk about. If you do not understand the diagrams, just read the text. Explanation of the rest is on its way.

about us as best we can and to use that understanding creatively. This is what we want to share with you.

Organic compounds

Organic chemistry started as the chemistry of life, when that was thought to be different from the chemistry in the laboratory. Then it became the chemistry of carbon compounds, especially those found in coal. But now it is both. It is the chemistry of the compounds formed by carbon and other elements such as are found in living things, in the products of living things, and wherever else carbon is found.

The most abundant organic compounds are those present in living things and those formed over millions of years from dead things. In earlier times, the organic compounds known from nature were those in the 'essential oils' that could be distilled from plants and the alkaloids that could be extracted from crushed plants with acid. Menthol is a famous example of a flavouring compound from the essential oil of spearmint and *cis*-jasmone an example of a perfume distilled from jasmine flowers.

Natural products have long been used to cure diseases, and in the sixteenth century one became famous—quinine was extracted from the bark of the South American cinchona tree and used to treat fevers, especially malaria. The Jesuits who did this work (the remedy was known as 'Jesuit's bark') did not of course know what the structure of quinine was, but now we do. More than that, the molecular structure of quinine has inspired the design of modern drug molecules which treat malaria much more effectively than quinine itself.

The main reservoir of chemicals available to the nineteenth century chemists was coal. Distillation of coal to give gas for lighting and heating (mainly hydrogen and carbon monoxide) also gave a brown tar rich in aromatic compounds such as benzene, pyridine, phenol, aniline, and thiophene.

■ At the other end of this book (Chapter 42) you will read about the extraordinary chemistry that allows life to exist—facts that are known only from cooperation between chemists and biologists.

menthol

cis-jasmone
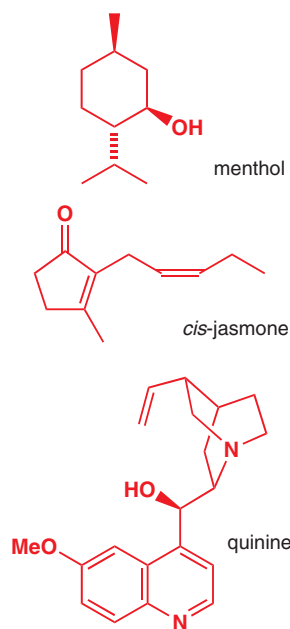
quinine
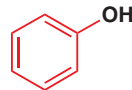
benzene   pyridine   phenol   aniline   thiophene

Phenol was used in the nineteenth century by Lister as an antiseptic in surgery, and aniline became the basis for the dyestuffs industry. It was this that really started the search for new organic compounds made by chemists rather than by nature. In 1856, while trying to make quinine from aniline, an 18-year old British chemist, William Perkin, managed to produce a mauve residue, mauveine, which revolutionized the dyeing of cloth and gave birth to the synthetic dyestuffs industry. A related dyestuff of this kind—still available—is Bismarck Brown: much of the early work on dyes was done in Germany.

Perkin was studying in London with the great German chemist, Hofmann. Perkin's attempt to make quinine this way was a remarkable practical challenge given that its structure was still unknown.

One of the constituents of mauveine

Bismarck Brown Y
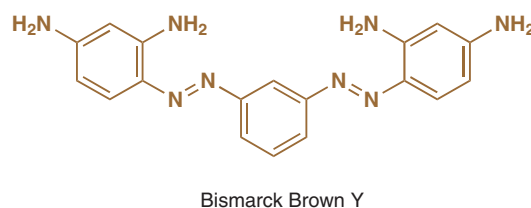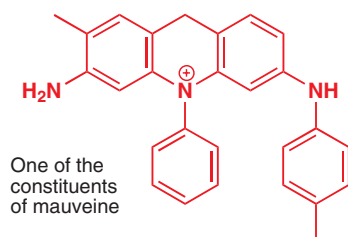
In the twentieth century oil overtook coal as the main source of bulk organic compounds so that simple hydrocarbons like methane (CH_4, 'natural gas'), propane, and butane ($CH_3CH_2CH_3$ and $CH_3CH_2CH_2CH_3$, 'calor gas' or LPG) became available for fuel. At the same time chemists began the search for new molecules from new sources such as fungi, corals, and bacteria, and two organic chemical industries developed in parallel—'bulk' and
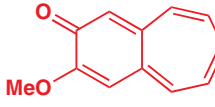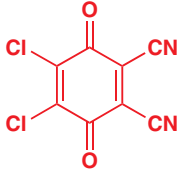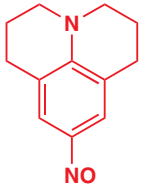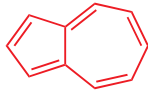
'fine' chemicals. Bulk chemicals like paints and plastics are usually based on simple molecules produced in multitonne quantities while fine chemicals such as drugs, perfumes, and flavouring materials are produced in smaller quantities but much more profitably.

At the time of writing there were over 16 million organic compounds known. How many more might there be? Even counting only moderately sized molecules, containing fewer than about 30 carbon atoms (about the size of the mauveine structure above), it has been calculated that something in the region of 1,000,000,000,000,000,000,000,000,000,000,000,000, 000,000,000,000,000,000,000,000 (10^{63}) stable compounds are possible. There aren't enough carbon atoms in the universe to make them all.

Among the 16 million that have been made, there are all kinds of molecules with amazingly varied properties. What do they look like? They may be crystalline solids, oils, waxes, plastics, elastics, mobile or volatile liquids, or gases. Familiar ones include sugar, a cheap natural compound isolated from plants as hard white crystals when pure, and petrol, a mixture of colourless, volatile, flammable hydrocarbons. Isooctane is a typical example and gives its name to the octane rating of petrol.
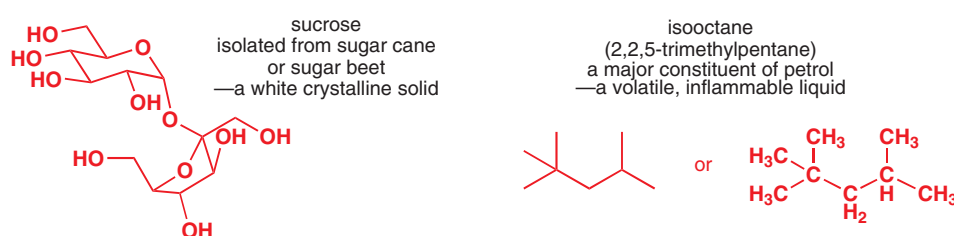
The compounds need not lack colour. Indeed we can soon dream up a rainbow of organic compounds covering the whole spectrum, not to mention black and brown. In this table we have avoided dyestuffs and have chosen compounds as varied in structure as possible.

Colour	Description	Compound	Structure
red	dark red hexagonal plates	3-methoxybenzocycloheptatriene-2-one	
orange	amber needles	dichlorodicyanoquinone (DDQ)	
yellow	toxic yellow explosive gas	diazomethane	
green	green prisms with a steel-blue lustre	9-nitrosojulolidine	
blue	deep blue liquid with a peppery smell	azulene	
purple	deep blue gas condensing to a purple solid	nitrosotrifluoromethane	

skunk spray contains:

thioacetone

propane-dithiol

4-methyl-4-sulfanylpentan-2-one

two candidates for the worst smell in the world (no-one wants to find the winner)

deliberately added to make natural gas smell 'like gas'

tert-butylthiol

the scent of the black truffle

damascenone—the smell of roses
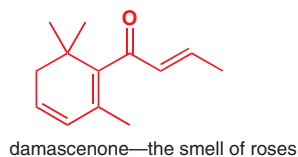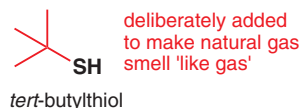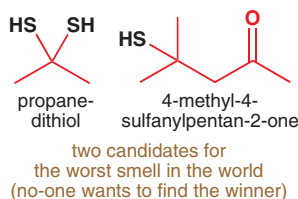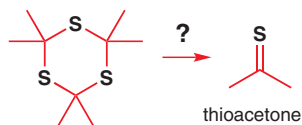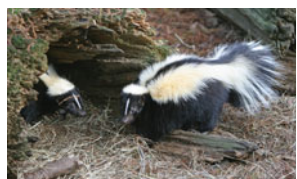
Colour is not the only characteristic by which we recognize compounds. All too often it is their odour that lets us know they are around. There are some quite foul organic compounds too; the infamous stench of the skunk is a mixture of two thiols—sulfur compounds containing SH groups.

But perhaps the worst smell ever recorded was that which caused the evacuation of the German city of Freiburg in 1889. Attempts to make thioacetone by the cracking of trithioacetone gave rise to 'an offensive smell which spread rapidly over a great area of the town causing fainting, vomiting, and a panic evacuation...the laboratory work was abandoned'.

It was perhaps foolhardy for workers at an Esso research station to repeat the experiment of cracking trithioacetone south of Oxford in 1967. Let them take up the story. 'Recently we found ourselves with an odour problem beyond our worst expectations. During early experiments, a stopper jumped from a bottle of residues, and, although replaced at once, resulted in an immediate complaint of nausea and sickness from colleagues working in a building two hundred yards away. Two of our chemists who had done no more than investigate the cracking of minute amounts of trithioacetone found themselves the object of hostile stares in a restaurant and suffered the humiliation of having a waitress spray the area around them with a deodorant. The odours defied the expected effects of dilution since workers in the laboratory did not find the odours intolerable ... and genuinely denied responsibility since they were working in closed systems. To convince them otherwise, they were dispersed with other observers around the laboratory, at distances up to a quarter of a mile, and one drop of either acetone *gem*-dithiol or the mother liquors from crude trithioacetone crystallizations were placed on a watch glass in a fume cupboard. The odour was detected downwind in seconds.'

There are two candidates for this dreadful smell—propane dithiol (called acetone *gem*-dithiol above) or 4-methyl-4-sulfanylpentan-2-one. It is unlikely that anyone else will be brave enough to resolve the controversy.

But nasty smells have their uses. The natural gas piped into homes contains small amounts of deliberately added sulfur compounds such as *tert*-butyl thiol $(CH_3)_3CSH$. When we say small, we mean *very small*—humans can detect one part in 50,000,000,000 parts of natural gas.

Other compounds have delightful odours. To redeem the honour of sulfur compounds we must cite the truffle, which pigs can smell through a metre of soil and whose taste and smell is so delightful that truffles cost more than their weight in gold. Damascenones are responsible for the smell of roses. If you smell one drop you will be disappointed, as it smells rather like turpentine or camphor, but next morning you, and the clothes you were wearing, will smell powerfully of roses. Many smells develop on dilution.

Humans are not the only creatures with a sense of smell. We can find mates using all our senses, but insects cannot do this. They are small in a crowded world and they find those of the opposite sex of their own species by smell. Most insects produce volatile compounds that can be picked up by a potential mate in incredibly weak concentrations. Only 1.5 mg of serricornin, the sex pheromone of the cigarette beetle, could be isolated from 65,000 female beetles—so there isn't much in each beetle. Nevertheless, the slightest whiff of it causes the males to gather and attempt frenzied copulation. The sex pheromone of the beetle *Popilia japonica*, also given off by the females, has been made by chemists. As little as 5 µg (micrograms, note!) was more effective than four virgin females in attracting the males.

serricornin
the sex pheromone of the cigarette beetle
Lasioderma serricorne

japonilure
the sex pheromone of the Japanese beetle
Popilia japonica
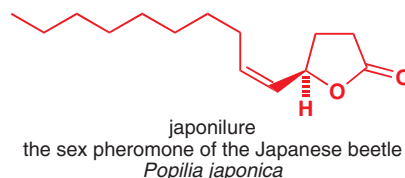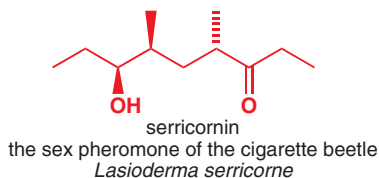
The pheromone of the gypsy moth, disparlure, was identified from a few µg isolated from the moths: as little as 2×10^{-12} g is active as a lure for the males in field tests. The three pheromones we have mentioned are available commercially for the specific trapping of these destructive insect pests.

disparlure
the sex pheromone
of the gypsy moth
Portheria dispar

olean
sex pheromone
of the olive fly
Bacrocera oleae
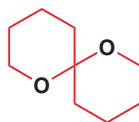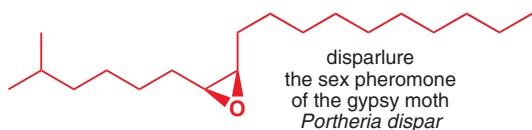
Gypsy moth

Don't suppose that the females always do all the work; both male and female olive flies produce pheromones that attract the other sex. The remarkable thing is that one mirror image of the molecule attracts the males while the other attracts the females! Mirror image isomers of a molecule called frontalin are also emitted by male elephants; female elephants can tell the age and appeal of a potential mate from the amount of each isomer he produces.

this mirror image
isomer attracts
male olive flies

this mirror image
isomer attracts
female olive flies

this mirror image
isomer smells of
young male elephant*

this mirror image
isomer smells of
old male elephant*

*if you are a
female elephant

What about taste? Take the grapefruit. The main flavour comes from another sulfur compound and human beings can detect 2×10^{-5} parts per billion of this compound. This is an almost unimaginably small amount equal to 10^{-4} mg per tonne or a drop, not in a bucket, but in a fairly large lake. Why evolution should have left us so extraordinarily sensitive to grapefruit, we leave you to imagine.

flavouring principle of grapefruit
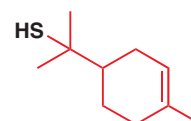
For a nasty taste, we should mention 'bittering agents', put into dangerous household substances like toilet cleaner to stop children drinking them by accident. Notice that this complex organic compound is actually a salt—it has positively charged nitrogen and negatively charged oxygen atoms—and this makes it soluble in water.

'denatonium benzoate', marked as Bitrex
benzyldiethyl[(2,6-xylylcarbamoyl)methyl]ammonium benzoate
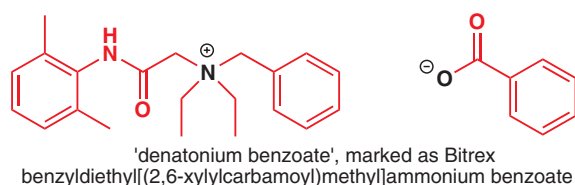
Other organic compounds have strange effects on humans. Various 'drugs' such as alcohol and cocaine are taken in various ways to make people temporarily happy. They have their dangers. Too much alcohol leads to a lot of misery and any cocaine at all may make you a slave for life.

alcohol
(ethanol)

MDMA
(ecstasy)

cocaine—an addictive alkaloid
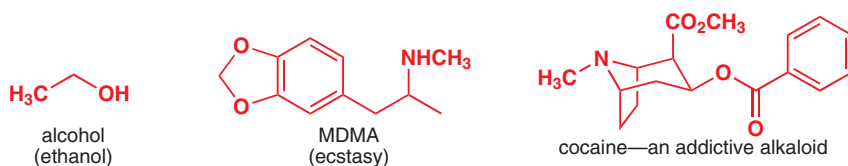
Again, let's not forget other creatures. Cats seem to be able to go to sleep anywhere, at any time. This surprisingly simple compound, isolated from the cerebrospinal fluid of cats, appears to be part of their sleep-control mechanism. It makes them, or rats, or humans fall asleep immediately.

cis-9,10-octadecenoamide
a sleep-inducing fatty acid derivative

CLA (Conjugated Linoleic Acid)
cis-9-*trans*-11 conjugated linoleic acid
dietary anticancer agent

resveratrole
from the skins
of grapes

vitamin C (ascorbic acid)
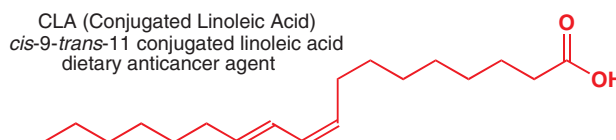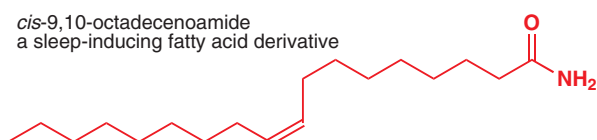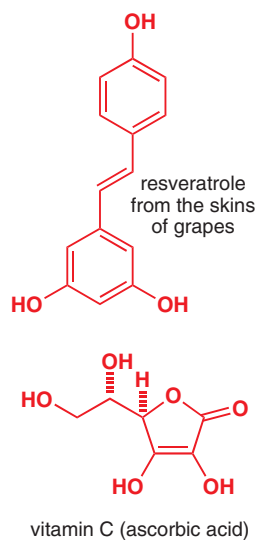
This compound and disparlure (above) are both derivatives of fatty acids. Fatty acids in the diet are a popular preoccupation, and the good and bad qualities of saturates, monounsaturates, and polyunsaturates are continually in the news: one of the many dietary molecules reckoned to have demonstrable anticancer activity is CLA (conjugated linoleic acid), which is found in dairy products and also, most abundantly, you may be interested to know, in kangaroo meat.

Resveratrole is another dietary component with beneficial effects: it may be responsible for the apparent ability of red wine to prevent heart disease. It is a quite different sort of organic compound, with two benzene rings.

For a third edible molecule, how about vitamin C? This is an essential factor in your diet—that is why it is called a vitamin—and in the diet of other primates, guinea-pigs, and fruit bats (other mammals possess the biochemical machinery to make it themselves). The disease scurvy, a degeneration of soft tissues from which sailors on the long voyages of past centuries suffered, results from a lack of vitamin C. It also is a universal antioxidant, scavenging for rogue reactive radicals and protecting damage to DNA. Some people think an extra large intake may even protect against the common cold.

Organic chemistry and industry

Vitamin C is manufactured on a huge scale by Roche, a Swiss company. All over the world there are chemistry-based companies making organic molecules on scales varying from a few kilograms to thousands of tonnes per year. This is good news for students of organic chemistry: knowing how molecules behave and how to make them is a skill in demand, and it is an international job market.

The petrochemicals industry consumes huge amounts of crude oil: the largest refinery in the world, in Jamnagar, India, processes 200 million litres of crude oil every day. An alarmingly large proportion of this is still just burnt as fuel, but some of it is purified or converted into organic compounds for use in the rest of the chemical industry.

Some simple compounds are made both from oil and from plants. The ethanol used as a starting material to make other compounds in industry is largely made by the catalytic hydration of ethylene from oil. But ethanol is also used as a fuel, particularly in Brazil, where it is made by fermentation of sugar cane. Plants are extremely powerful organic chemical factories (with sugar cane being among the most efficient of all of them). Photosynthesis extracts carbon dioxide directly from the air and uses solar energy to reduce it to form less oxygen-rich organic compounds from which energy can be re-extracted by combustion. Biodiesel is made in a similar way from the fatty acid components of plant oils.

ethyl stearate (ethyl octadecanoate), a major component of biodiesel
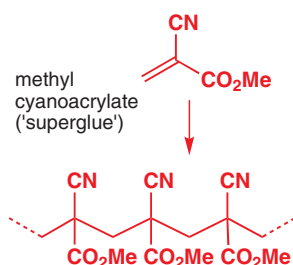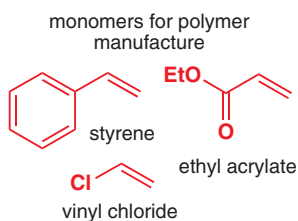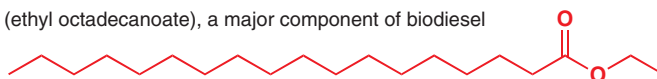
Plastics and polymers take much of the production of the petrochemical industry in the form of monomers such as styrene, acrylates, and vinyl chloride. The products of this enormous industry are everything made of plastic, including solid plastics for household goods and furniture, fibres for clothes (over 25 million tonnes per annum), elastic polymers for car tyres, light bubble-filled polymers for packing, and so on. Worldwide 100 million tonnes of polymers are made per year and PVC manufacture alone employs over 50,000 people to make over 20 million tones per year.

Many adhesives work by polymerization of monomers, which can be applied as a simple solution. You can glue almost anything with 'superglue', a polymer of methyl cyanoacrylate.
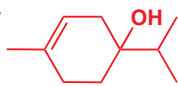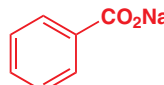
Washing-up bowls are made of the polymer polyethylene but the detergent you put in them belongs to another branch of the chemical industry—companies like Unilever and Procter and Gamble produce detergent, cleaners, bleaches, and polishes, along with soaps, gels, cosmetics, and shaving foams. These products may smell of lemon, lavender, or sandalwood but they too mostly come from the oil industry.

Products of this kind tend to underplay their petrochemical origins and claim affinity with the perceived freshness and cleanliness of the natural world. They also try to tell us, after a

monomers for polymer
manufacture

styrene

ethyl acrylate

vinyl chloride

methyl
cyanoacrylate
('superglue')

fashion, what they contain. Try this example—the list of contents from a well-known brand of shower gel, which we are reassuringly told is 'packed with natural stuff' (including 10 'real' lemons) and contains '100% pure and natural lemon and tea tree essential oils'.

It doesn't all make sense to us, but here is a possible interpretation. We certainly hope this book will set you on the path of understanding the sense (and the nonsense!) of this sort of thing.
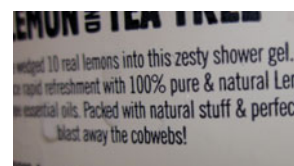
Ingredient	Chemical meaning	Purpose
aqua	**H–O–H** water	solvent
sodium laureth sulfate	$C_{12}H_{25}$–(O)$_n$–OSO$_3$Na typically $n = 3$	detergent
cocamide DEA	$C_{11}H_{23}$ (with N, two OH)	foaming agent
Citrus medica limonum peel oil	mainly α-pinene	scent, appeal to customer
Melaleuca alternifolia leaf oil	mainly terpinen-4-ol	scent, appeal to customer, possibly antiseptic
glycerin	HO–…(OH)…–OH glycerol	cosolvent; moisturizer; ensures smoothness
cocamidopropyl betaine	$C_{11}H_{24}$ (amide, N$^+$, O$^-$)	detergent and anti-electrostatic
sodium chloride	**NaCl**	control solubility of Na$^+$-based detergents
lactic acid	OH, CO$_2$H	acidifier
styrene acrylates copolymer	[Ph]$_n$[CO$_2$R]$_m$ R = Me or H	film former
tetrasodium glutamate diacetate	NaO$_2$C, CO$_2$Na, NaO$_2$C–N–CO$_2$Na	chelator, to prevent formation of insoluble scum in hard water
sodium benzoate	CO$_2$Na	preservative

PEG/PPG -120/10
trimethylolpropane
trioleate

R^1 = H or Me
R^2 = —$(CH_2)_7$ $(CH_2)_7CH_3$

viscosity controller

laureth-2 $C_{12}H_{26}$ emulsifier

benzotriazolyl
dodecyl *p*-cresol $C_{12}H_{25}$ absorbs UV light

BHT   antioxidant

citral   lemon fragrance

mixture of isomers

limonene   lemon fragrance

CI 19140   yellow colouring

tartrazine

CI14700   colouring

Scarlet GN
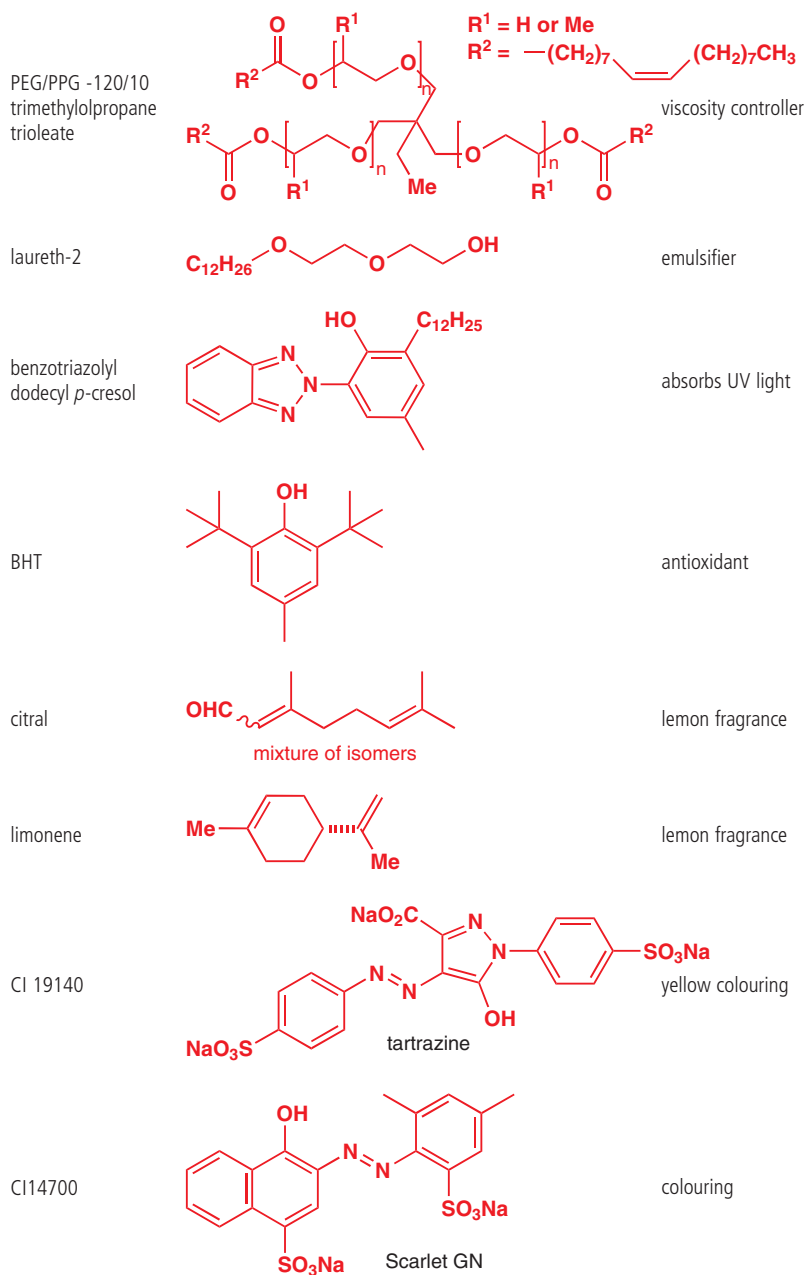
The particular detergents, surfactants, acids, viscosity controllers, and so on are chosen to blend together to give a smooth gel. The result should feel, smell, and look attractive and work as an effective detergent and shampoo (some of the compounds are added for their moisturizing and anti-electrostatic effect on hair). The yellow colour and lemon scent are considered fresh and clean by the customer. Several of the ingredients are added as pure compounds; the ones which aren't are mixtures of isomers or polymers; the most impure are the mixtures of hydrocarbons referred to as the 'pure and natural' essential oils. Is it 'packed with natural stuff'? Indeed it is. It all comes from natural sources, the principal one being decomposed carboniferous forests trapped for millions of years underground.

The coloration of manufactured goods is a huge business, with a range of intense colours required for dyeing cloth, colouring plastic and paper, painting walls, and so on. Leaders in this area are companies such as Akzo Nobel, which had sales of €14.6 bn in 2010. One of the most commonly used dyestuffs is indigo, an ancient dye that used to be isolated from plants but is now made from petrochemical feedstocks. It is the colour of blue jeans. More modern

dyestuffs can be represented by the benzodifuranones developed by ICI, which are used for colouring synthetic fabrics like polyesters (red), the phthalocyanine–metal complexes (typically blue or green), or the 'high-performance' red pigment DPP (1,4-diketopyrrolo[3,4-c]pyrroles) series developed by Ciba-Geigy.

indigo
the colour of blue jeans

ICI's Dispersol
benzodifuranone
red dyes for polyester

ICI's Monastral Green GNA
a green for plastic objects

Ciba-Geigy's Pigment Red 254
an intense DPP pigment
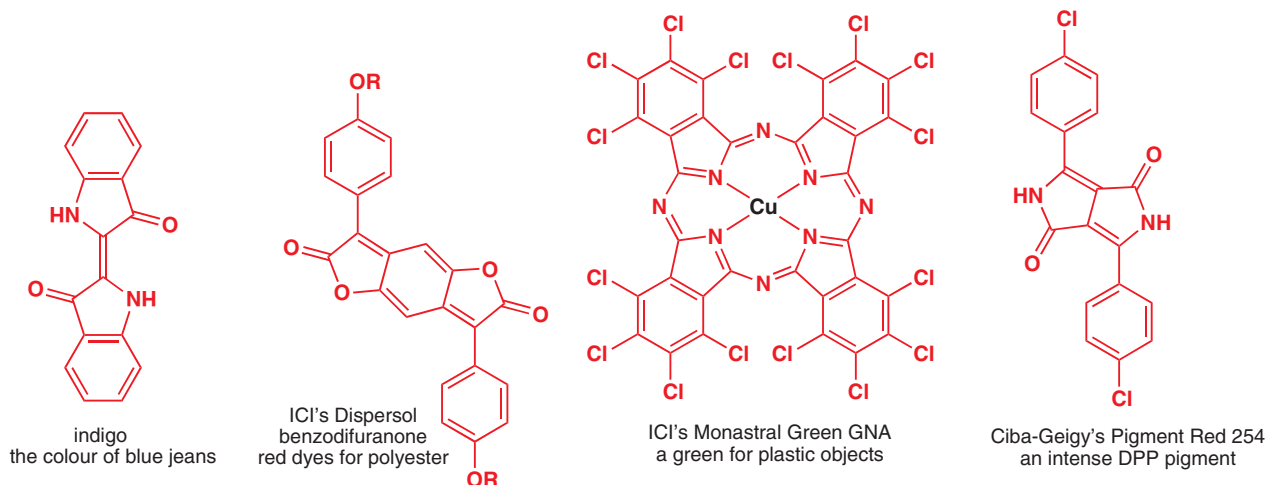
The scent of the shower gel above came from a mixture of plant extracts with the pure compound (in fact a mixture of two isomers) citral. The big fragrance and flavouring companies (such as Firmenich, International Flavors and Fragrances, and Givaudan) deal in both naturals and synthetics—'naturals' are mixtures of compounds extracted from plants—leaves, seeds, and flowers. 'Synthetics' are single compounds, sometimes present in plant-derived sources and sometime newly designed molecules, which are mixed with each other and with 'naturals' to build up a scent. A typical perfume will contain 5–10% fragrance molecules in an ethanol/water (about 90:10) mixture. So the perfumery industry needs a very large amount of ethanol and, you might think, not much perfumery material. In fact, important fragrances like jasmine are produced on a >10,000 tonnes per annum scale. The cost of a pure perfume ingredient like *cis*-jasmone (p. 2), the main ingredient of jasmine, may be several hundred pounds, dollars, or euros per gram.

The world of perfumery

Perfume chemists use extraordinary language to describe their achievements: 'PacoRabanne pour homme was created to reproduce the effect of a summer walk in the open air among the hills of Provence: the smell of herbs, rosemary and thyme, and sparkling freshness with cool sea breezes mingling with warm soft Alpine air. To achieve the required effect, the perfumer blended herbaceous oils with woody accords and the synthetic aroma chemical dimethylheptanol, which has a penetrating but indefinable freshness associated with open air or freshly washed linen.'

Chemists produce synthetic flavourings such as 'smoky bacon' and even 'chocolate'. Meaty flavours come from simple heterocycles such as alkyl pyrazines (present in coffee as well as roast meat) and furonol, originally found in pineapples. Compounds such as corylone and maltol give caramel and meaty flavours. Mixtures of these and other synthetic compounds can be 'tuned' to taste like many roasted foods from fresh bread to coffee and barbecued meat. Some flavouring compounds are also perfumes and may also be used as an intermediate in making other compounds. Vanillin is the main component of the flavour of vanilla, but is manufactured on a large scale for many other uses too.

an alkyl pyrazine
from coffee and
roast meat

furonol
roast meat

corylone
caramel
roasted taste

maltol
E-636 for cakes
and biscuits

vanillin
found in vanilla pods;
manufactured on a large scale